Research methods for critical care

de Grooth, H.J.S.

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General introduction

The aim of all critical care research is ultimately to answer variants of the same question: How can we improve the outcomes of patients with specific critical illness-associated diagnoses? To answer such questions, clinical researchers have at their disposal a vast instrumentarium of definitions, statistical tools and the most data-rich patient population in the hospital. But despite enormous efforts, the results over the last decades have been disappointing.

In the last 40 years, sepsis and septic shock have been the focus of more than 100,000 research publications [1,2] and more than 2,000 randomized controlled trials [3,4]. Hundreds of millions – if not billions – of Euros have been spent on the development and testing of pharmaceutical agents and interventions. But these efforts have not resulted in a single novel intervention to treat sepsis and its devastating consequences [5,6]. In the same 40 years, the Acute Respiratory Distress Syndrome (ARDS) and positive pressure ventilation have been the subject of more than 70,000 research publications [7] and more than 5,000 randomized controlled trials [8]. All of this research has resulted in a single consensus intervention (low tidal volume ventilation [9]) and a handful of debated adjunctive therapies [10].

The bleak results for sepsis and ARDS extend to most aspects of critical care research, from acute kidney injury to delirium or post-cardiac arrest syndrome. No critical care diagnosis has seen a treatment revolution in the last decades based on 'level A' evidence [5,6,11], and many once-promising results could not be reproduced [12]. This paucity of strong evidence is also reflected in clinical practice guidelines such as the Surviving Sepsis Campaign, whose recommendations are based for 62% on low or very low-level evidence [13,14]. The poor return on research investment has led several leading investigators to question the current research paradigm, or – more radically – to call for a total abandonment of randomized controlled trials with mortality endpoints in critical care [6,15–17].

There are, however, more hopeful data. Several very large observational studies have found that the overall mortality rate of sepsis has decreased substantially since 1980 [18–21]. In one of the most detailed of these studies with more than 100,000 severe sepsis patients in Australia and New Zealand, the adjusted mortality rate decreased by half between 2000 and 2012 [21]. There appears to be a similar improvement in the mortality rate of ARDS over time [22,23], although one study reports a stagnation since the mid 1990's [24]. The mortality rate of (non-sepsis, non-ARDS) intensive care patients appears to have decreased overall [21,25]. In the absence of strong evidence for any beneficial treatment, it is hard to determine what caused this improvement in outcomes, but it is likely to be at least partly attributable to improved safety standards, earlier detection of severe illness and a faster response to the deteriorating patient [16].

If indeed there has been progress in the quality of critical care over the last decades, it seems not to have originated in mortality-reducing randomized controlled trials. This stands in sharp contrast with the progress in medical oncology and hematology, where most progress has a foundation in therapies with a proven benefit in clinical trials. Yet substantial improvements in outcomes can be attained without such trials, as we also know from a field

closely related to critical care: Through a relentless focus on perioperative safety, anesthesia-related mortality has decreased more than tenfold without a single large randomized controlled trial demonstrating a mortality benefit [26].

We should therefore shy away from the reductionist perspective that progress in the treatment of critically ill patients must necessarily originate from large randomized controlled trials. But alternative approaches to the epistemology of therapeutic benefit are not so clear: Without the obviously relevant anchor of a reduced mortality rate, how can we know which therapies are truly beneficial and which therapies merely polish the numbers, ratios and lab results without actually improving the long-term outcomes of our patients?

The work presented in this thesis is the result of questions that came up during the design of several clinical studies. Two of these studies are included as a preamble to the main body – not because they solve any methodological question but rather to illustrate how methodological choices are fundamentally tied to clinical questions. On a more personal level, these studies are included here to reflect how applied clinical research led me to investigate several common design choices in critical care studies. The first of these studies (**chapter 1**) is a randomized controlled pharmacokinetic trial investigating the dose-plasma concentration relationship for high-dose intravenous vitamin C. This study is included here because the vitamin C research line – with a large randomized trial as an end goal – led us to question both the optimal study endpoint and the optimal study population for a future large randomized controlled trial. **Chapter 2** is an abridged study protocol for the O_2-ICU trial, the randomized study that has been my largest clinical research effort in the last years. The protocol is included here because the choice of the primary endpoint led us to investigate the utility of surrogate endpoints.

The chapters grouped as Part I are focused on the validity of several commonly accepted endpoints in critical care trials. In **chapter 3** we explain the difference between so-called disease-oriented endpoints and patient-oriented endpoints, and we demonstrate that disease-oriented endpoints have become increasingly more prevalent in critical care research over the past decades. We explain why a strong association between a disease-oriented endpoint (e.g. SOFA score) and a patient-oriented endpoint (e.g. mortality) is a necessary but not sufficient condition for the validity of the disease-oriented endpoint (the surrogate paradox). In **chapter 4** we aimed to investigate the validity of different SOFA score derivatives as endpoints using data from 87 published randomized trials with a SOFA endpoint. We show that a four-quadrant plot of treatment effects on SOFA score versus treatment effects on mortality (and accompanying weighted mixed effects model) is a convenient way to evaluate whether a surrogate adequately captures effects on mortality. We then applied these methods to another research field with multiple interchangeably used endpoints: Studies aiming to reduce central venous catheter-associated infections. In **chapter 5** we set out to investigate the validity of various endpoints used in catheter-related infection studies using

study-level data from 70 trials and individual-level data of 9428 catheters from four of the largest randomized trials in this field.

After this work on questions surrounding trial endpoints, we change focus to questions surrounding trial populations. The chapters grouped as Part II of this thesis are focused on an archetypical study population in critical case research: Patients with septic shock. We observed that many septic shock trials show conflicting results and in **chapter 6** we wanted to answer the question: How similar are the populations of different randomized trials with septic shock patients? Using data from 56 septic shock trials and multiple statistical techniques we arrived at surprising results. These findings have important consequences for reporting standards and for the external validity of septic shock trials, as we briefly argue in **chapter 7**. In **chapter 8**, we investigated whether a higher control-group mortality rate (and especially an unexplainably high control-group mortality rate) is associated with 'positive' ($p<0.05$) results in septic shock trials. In **chapter 9** we tried to quantify (using Monte Carlo simulation methods) how syndrome-attributable risk influences the chance of detecting a beneficial effect on mortality in large randomized controlled trials.

The papers grouped under Part III are focused on the interface between statistical significance and clinical relevance. In **chapter 10** we investigated whether regression methods applied to observational data can be used to properly 'control for' variables strongly influencing the outcome of interest. In critically ill patients, treatment dose or intensity is often positively or negatively related to the underlying severity of illness and consequent mortality risk, while overtreatment or undertreatment (relative to the individual need) may further increase the odds of death. Examples are vasopressor dose, fluid balance or (successful) enteral feeding dose. Using Monte Carlo Simulation methods, we investigated how such relations are reflected in common statistical methods. In **chapter 11** (an editorial on a study about the prognostic value of biomarkers for acute kidney injury) we explain how risk stratification is often confused for discrimination and discuss the limitations of the Area Under the Receiver Operator Characteristics Curve (AUROC) in this context. In **chapter 12** we critically reviewed the literature on Early Warning Scores in the perioperative period and we evaluated whether the AUROC, although it is the most often used performance metric, provides a practically useful evaluation of the performance of early warning scores. The overarching point of the papers in Part III is that statistical techniques applied without a proper basis in clinical concepts will often lead to unreliable results.

In all, this thesis is about critical care research instruments in the broadest sense: About trial endpoints, study populations and statistical methods. What connects the different subjects and papers is the idea that, rather than theorizing about the validity and usefulness of an instrument, we can and should evaluate these instruments empirically using real-world data. With the help of many others, I have attempted to do this for several small subsections

of the vast research landscape. I hope this work contributes to improved efficiency, more transparent statistical reporting and better reproducibility in critical care research.

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